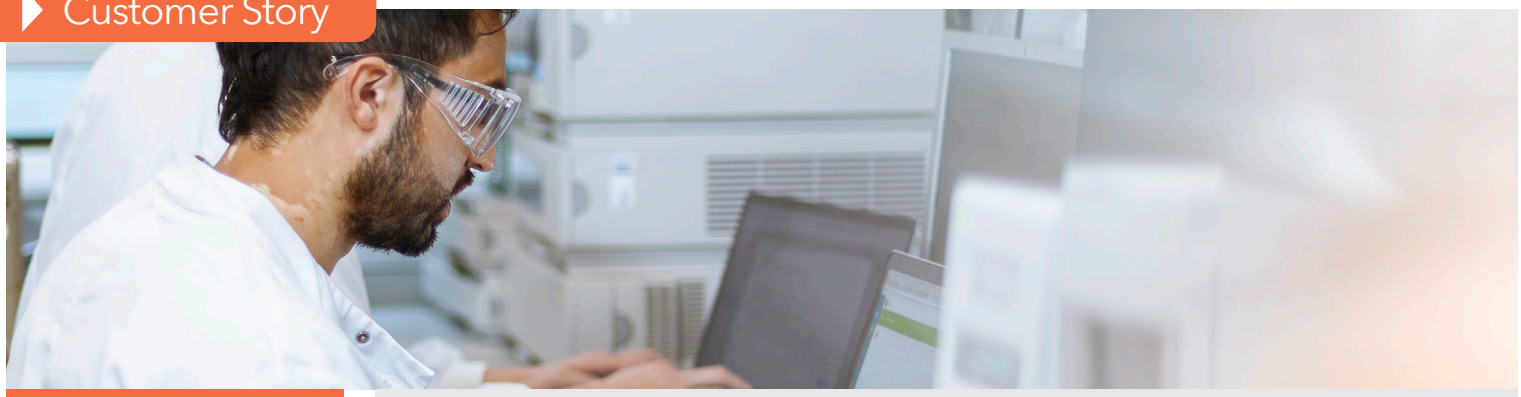
Customer Story



SYNTHACE

Challenge

Life scientists have often taken a manual, one-factor-at-a-time approach to experimentation that omits critical insights into how simultaneous changes in multiple factors can affect the biological outcomes. In the face of increasingly complex methodologies and research questions, a more comprehensive approach is required.

Engineering biology: Synthace accelerates R&D by lowering barriers to automated experiments

Synthace's cloud-based platform Antha® enables automation of design of experiments (DOE) to optimize complex biological processes and assays. Its seamless integration with JMP® software helps biologists achieve all the benefits of sophisticated statistical methods without time-intensive programming.

Biology holds infinite potential for improving human health, developing cleaner chemicals and fuels, advancing environmental sustainability and more. And all that promise begins with experimentation. With the advent of laboratory automation and more rigorous analytical techniques, scientists now have the opportunity to ask more complex questions to understand and develop more complex biological systems. However, even high-throughput one-factor-at-a-time approaches are insufficient to meet the ambitious timelines and scientific objectives of modern life science and bioprocessing laboratories. More importantly, critical insights can be missed when the impact of simultaneous changes in multiple factors is not being observed.

Technology has advanced to give scientists the software and instrumentation to conduct multifactorial experiments and thereby improve their overall statistical power and reproducibility. However, these scientists don't often have the time to gain the statistical and automation expertise needed to take full advantage of the available tools. Solving this challenge is the goal of Synthace, an interdisciplinary team of computer scientists, biologists, chemists and mathematicians. Founded in London in 2011, the company is developing more intuitive ways to digitize – and industrialize – the future of biology.

Automated experiments boost precision and reproducibility

Synthace's proprietary cloud-based platform, Antha, provides an automated architecture for experimentation and analysis. On the experimentation side, this enables fast, codeless programming of liquid handlers, as well as visual previews and error checking before experiment execution.

"Biological systems can often be quite noisy, and a lot of assays tend to be very labor- and resource-intensive," explains Michael Sadowski, PhD, Head of Bioinformatics at Synthace. "That can impose a lot of constraints on how big an experiment you can do if you're doing everything by hand." Antha not only resolves the problem of pace in manual experimentation but also facilitates for higher precision and reproducibility.

Manual processes introduce additional issues. One is that scientists tend to create ad hoc spreadsheet-based tools that, though useful for specific use cases, are time-consuming and error-prone to modify for future experiments. Another is that crucial contextual data, such as instrument configurations and environmental conditions, are often lost in the shuffle. "There's a lot of administrative burden involved in capturing data and putting it in the right context," Sadowski says. "You typically interact with dozens of different machines, all of which have their own interfaces and data formats. Then you have to wrangle all that into your analysis software."

More than just automating execution, Antha enables automated data collection, structuring and visualization. It's a system that, Sadowski says, reduces human error and makes the science more reproducible vis-à-vis documentation and strict adherence to study protocols; an advantage that ultimately helps speed discovery. In a conventional laboratory setting, he explains, "there are things you don't realize you're doing and things you don't record that might be critical to the process. So other scientists can't later understand what you did. Studies show that it's rare to find enough information in a published paper to reproduce an experiment." Synthace is one of the companies at the forefront of an industrywide effort to solve this issue, with a recent white paper on the importance of complete data to reproducibility and fully realizing the benefit of experimental data.

Antha's developers early on saw the value in tackling the challenge of reproducibility through automation. But Synthace didn't stop there. What they are pursuing is a broad vision for applying computational methods to experimental problems, which they have coined as "Computer-Aided Biology." The vision of Computer-Aided Biology is to overcome the bottlenecks currently experienced when working with biological systems by creating software approaches to handle the large-scale data gathering, structuring, analysis and modeling required for understanding biology.

Automated DOE takes biology to the next level

"In the beginning, our solution focused only on mixing liquids with lab automation," Sadowski says. "But we quickly realized that there was a huge advantage if we were to express more of the process in a way that would allow it to be translated to automation." With its user-friendly, visual interface, Antha enables biologists to think of an experiment in terms of the biology behind it – without the distraction of the mechanical steps and statistical analyses that are a necessary part of the process. "[The system's output] is something that makes much more sense to biologists in biological terms," he adds. In other words, biology in, biology out.

Reducing the statistical burden on biologists, however, does not mean reducing the statistical power of the experimental design. By applying a sophisticated statistical approach known as design of experiments (DOE), Synthace's systems put statistical optimization at the heart of experimentation. DOE provides a structured approach to understanding complex systems such as biological processes and can be applied to a range of applications in research and discovery as well as bioprocess development. The goal is reducing time to scientific insight.

jmp® Statistical Discovery™ From SAS

> Biologists are at the beginning of a transition to a new way of conducting experiments… You don't merely look at questions in terms of the limited solutions you can implement by hand. You can focus on more problems and make sure the questions you're asking are the right ones. Computational tools like JMP and Antha are the way we can get there.
>
> Michael Sadowski, Head of Bioinformatics

DOE, Sadowski explains, reduces wasted experimental effort by exploring many factors in parallel – seeking to understand how they interact in a way that affects outcomes. Doing so both accelerates the pace of experimentation and reduces costs and resource utilization by decreasing the number of iterations needed overall. Without DOE, scientists tend to restrict the number of factors they investigate due to time and resource constraints.

"We have examples where we show that the success of the process we engineered was critically dependent on a three- or four-factor interaction," Sadowski says. "It's very hard to imagine how you'd get there without DOE. You need either a big flash of insight or serendipity if you're doing things in a more traditional way." Synthace's computer-aided approach to experimentation lowers the barriers to designing, running and analyzing such sophisticated, multifactorial experiments.

JMP® at the core

Even with an easy-to-use software platform like Antha to help with automation, a lack of statistical expertise could still deter biologists from optimizing bioprocesses with DOE. That is why Synthace has integrated Antha and JMP.

JMP, Sadowski explains, offers superior tools for DOE that make the software virtually indispensable for biologists using Antha for advanced multifactorial experiment. As the current gold standard DOE solution for industry, JMP is already being used by the majority of Synthace's clients. By interface directly with JMP, Synthace has augmented the benefits of using Antha: Now biologists have a one-stop shop for experimental design, execution and analysis.

The interactive graphical interface of JMP encourages data exploration and discovery – a step that helps scientists verify that experiments are running as expected and producing consistent results. "Visualization is absolutely essential," Sadowski says. "With experimental data, the first thing you have to do is visualize it. In some cases, it's the only thing you can do. We've had several cases where the first runs were noisier than expected. You couldn't build any model. But with visualization, you could see things that looked interesting and design your next experiment to determine more rigorously if they are real effects."

JMP tables containing design information are exported for input into Antha for execution. And afterward, Antha assembles and structures outputs as JMP data tables. Such experiments can be easily iterated within Antha to arrive at useful insights more quickly. Synthace is also constantly improving the user experience with better integrations – a new Antha feature currently in early-stage development uses JMP scripting language (JSL) to directly interface with JMP software's optimal design platform. This takes advantage of the power of Antha's execution and analysis workflows to unambiguously define the factors scientists may want to explore with DOE.

Reducing experimentation time and increasing product yields

Since the inception of the company, Synthace's application of DOE to bioprocess optimization has been critical to their success. One of the earliest successes was the optimization of the expression of a human drug metabolism enzyme in a microbial host in a campaign that achieved a twentyfold increase on published values in only four weeks of experimental time. Sadowski recalls, "the main reason that campaign succeeded is that using DOE allowed us to identify a three-factor interaction. It would have been almost impossible to do that any other way."

Synthace's partners have also achieved impressive results with the Antha architecture integrated with JMP. Seeking to improve the efficiency and robustness of their lentiviral vector production, Oxford BioMedica – a UK-based pioneer in gene and cell therapy – employed Antha to design and execute multifactorial experimental approaches. Not only did the company report saving 40 hours in experimental planning, they achieved a threefold to tenfold increase in vector titer and reported an 81% reduction in pure error, thus indicating a more robust process.

Synthace's own lab, in partnership with liquid dispenser manufacturer SPT Labtech, was able to characterize a spectrophotometric enzymatic assay using a space-filling DOE, totaling 3,456 runs for two sets of triplicates of 384 runs and corresponding controls. A single user executed this DOE campaign in one day – and gained a wealth of data for future assay optimizations. The company also reduced the time spent on planning 20,745 liquid-handling steps by 75% and the time spent on data aggregation from the microplate reader by 94%.

"Biologists are at the beginning of a transition to a new way of conducting experiments," Sadowski says. "Up to now, they've had to approach experiments in terms of what each individual can do personally. But that's changing – and rapidly.

"Once you have computer-aided experiments, with software assisting with the planning, execution and analysis, it encourages you to think bigger. You don't merely look at questions in terms of the limited solutions you can implement by hand. You can focus on more problems and make sure the questions you're asking are the right ones. Computational tools like JMP and Antha are the way we can get there."

More broadly, the company sees this kind of experimentation as the tip of the iceberg: "There's something of an AI bubble in the industry at the moment, but the first problem you hit when trying to apply more sophisticated methods is the lack of clean data with the right structure and annotations to support ever more complex modelling. Implementing sophisticated designed experiments is essential for that to happen."

Solution

Synthace offers a new approach, by applying the principles of DOE, to reduce experimentation time and make biological research more reproducible. The company's Antha platform integrates seamlessly with JMP statistical discovery software. The system delivers fast, codeless programming of liquid handlers, visual execution previews and error checking, as well as user-friendly interfaces to plan and execute DOE campaigns and automated structuring and visualization of the experimental data and metadata.

Results

Payoffs include substantial time savings for experiment planning, execution and data aggregation. In one case, biologists at Oxford BioMedica used Antha in combination with JMP to realize a threefold to tenfold increase in viral vector titer in just two iterations of DOE with a reduced time frame. In another case, scientists at SPT Labtech reported reducing the time spent planning 20,745 liquid-handling steps by 75% and the time spent on data aggregation by 94%.

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